

THE EFFECTS OF CYCLICAL ESTROGEN ON BLADDER STRUCTURE

Hypothesis / aims of study

Estrogen is essential for physiological maintenance and integrity of the female urogenital tract. Alterations in circulating estrogen have been shown to have marked effects on the bladder of experimental animals. Ovariectomy induced smooth muscle and mucosal atrophy, increased collagen synthesis and deposition, decreased contractile function, and decreased mucosal and smooth muscle blood flow. Estrogen administration not only reversed these effects, but also increased bladder mass and smooth muscle density primarily by stimulating angiogenesis and increasing blood flow. Thus, estrogen has a clear and marked effect on bladder detrusor morphology and function. The specific aim of this study was to determine the effects of cycling estrogen in rabbits.

Study design, materials and methods

Twenty adult female NZW rabbits were divided into 5 groups of 4 rabbits each. Group 1 served as the control group. Groups 2 through 5 received bilateral ovariectomy. Group 2 (OVX) received no estradiol and was studied 2 weeks after ovariectomy. Groups 3 through 5 received 17- β estradiol by subcutaneous slow release tablet two weeks after ovariectomy and remained in place for a subsequent 2 week period. Group 3 (OVX + E) was then studied after this two weeks on estradiol. Groups 4 and 5 then had their estradiol tablets removed for a two week period and group 4 was studied after this two weeks off of estradiol. At this time, group 5 received a new estradiol tablet via subcutaneous implant and was left in place for an additional 2 week period.

Results

Both groups receiving estrogen (3 and 5) showed significant increases in bladder weight over both the control and Ovx groups. The volume fraction of smooth muscle paralleled the bladder weight showing that estrogen increased the volume fraction of smooth muscle (SM) while decreasing the volume fraction of connective tissue. Ovariectomy and low estrogen decreased the SM fraction and increased the volume fraction of connective tissue. The cross sections of the urethras from Groups 3 and 5 were significantly wider than either control or OVX also being consistent with the structural effects of estrogen. However, the volume fractions of smooth muscle and connective tissue of the urethra did not change. Ovx and reduced estrogen groups resulted in a decreased vascular density whereas both estrogen groups resulted in significant increases in vascular density (angiogenesis). Quantitation of the blood vessel circumferences demonstrated that the increase in vascular density was clearly due to increases in the number and distribution of microvessels, which supports the conclusion that the increased vascular density is due to the stimulation of angiogenesis. One interesting fact was that the increased vascular density was accompanied by a marked change in the distribution of blood vessels. The new blood vessels were distributed throughout the hypertrophied smooth muscle (between muscle cells and not just between bundles). However, there were no changes in vascular density or blood vessel circumferences in the urethra.

Interpretation of results

Cyclical estrogen had pronounced structural effects on the bladder, but only minimal effects on the urethra. This was an unexpected finding. The mucosa of the urethra seemed to be the only compartment that was sensitive to changes in circulating estrogen. The marked changes in vascular density in the bladder modulated by cyclical estrogen and the accompanying hypoxia induced during periods of low circulating estrogen may be detrimental to the sensory nerves localized in the submucosa and may be related to pain syndromes such as interstitial cystitis suffered primarily by women.

Concluding message

Cyclical periods of high and low estrogen mediate cyclical bladder smooth muscle hypertrophy / atrophy; and cyclical bladder angiogenesis / apoptosis (mediating the decreased vascular density). We believe that these structural changes that occur during the cyclical alterations in estrogen that occur during the menstrual cycle may play a role in the etiology of bladder dysfunctions that primarily affect women such as recurrent urinary tract infection and interstitial cystitis.

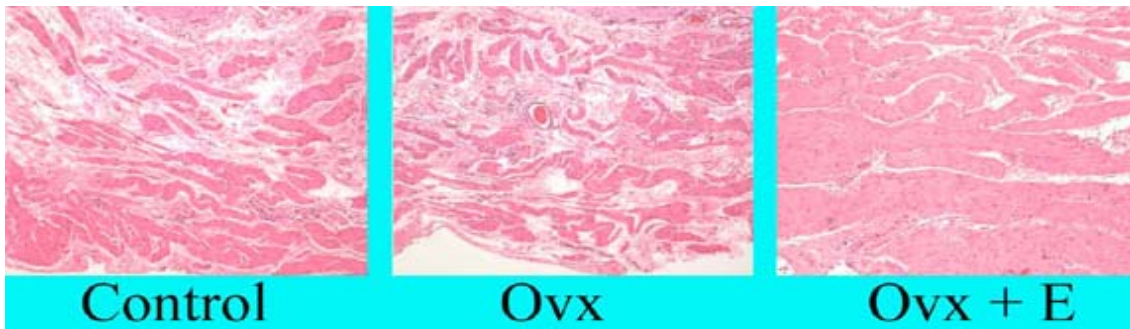


Figure 1:

Representative pictures of H&E stained sections showing atrophy of the smooth muscle in the ovariectomized bladder and smooth muscle hypertrophy in the estrogen treated bladders.

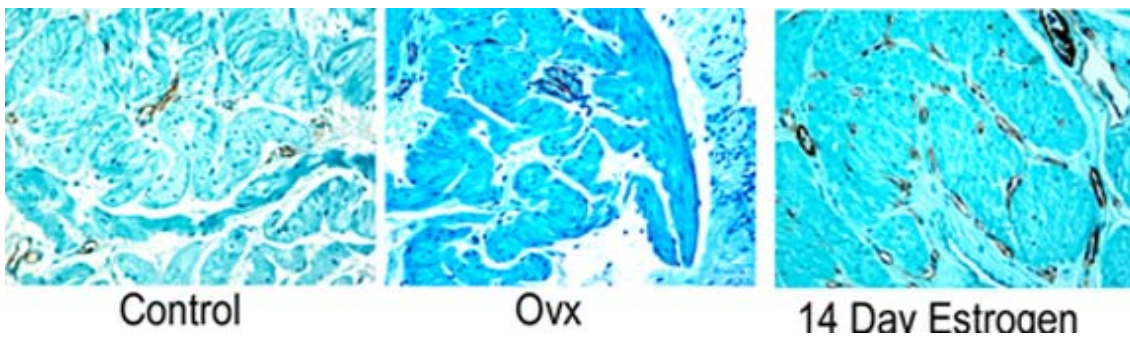


Figure 2: Representative immunohistograms showing vascular density via cd-31. One can notice the decreased vascular density in the ovariectomized and angiogenesis in the estrogen treated bladders.

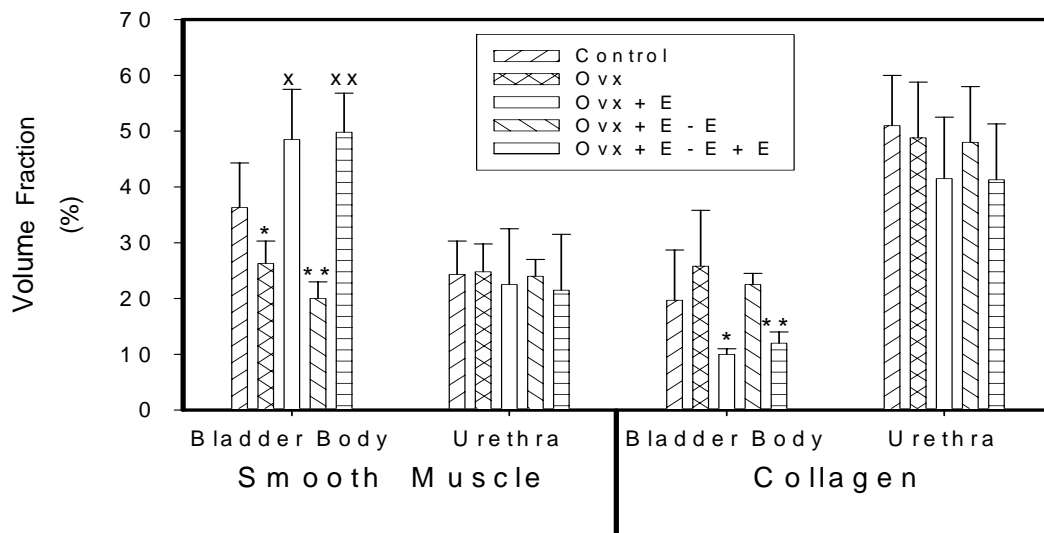


Figure 3: Effect of cyclical estrogen on volume fractions of smooth muscle and collagen. * = significantly different from control; ** = significantly different from Ovx + E; X = significantly different from Ovx; XX = significantly different from Ovx + e-E; p < 0.05

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ANIMAL SUBJECTS: This study followed the guidelines for care and use of laboratory animals and was approved by Stratton VAMC IACUC Committee